PATENT
ATTORNEY DOCKET NO.: **056291-5304**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **1864**
Stephen R. WEDGE	)	
Application No.: **10/594,234**	)	Group Art Unit: **1611**
Filed: **September 25, 2006**	)	Examiner: **Rae, Charlesworth E**
FOR: **COMBINATION THERAPY**	)	
	)	Date: **February 13, 2009**

SUBMISSION OF DECLARATION UNDER 37 CFR § 1.132

Supplemental to the Amendment and Response filed herein on December 18, 2008, submitted herewith is a **Declaration Under 37 C.F.R. 1.132 of Stephen R. Wedge**, verifying the data previously submitted and supporting arguments made in that December 18, 2008 Amendment and Response. This is the Declaration referred to at page 14 of that Amendment and Response that the undersigned undertook to provide as soon as it was available to him.

It is respectfully submitted that this Declaration be considered and taken into account together with Applicant's December 18, 2008 Amendment and Response when this application is next taken up for examination.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: February 13, 2009 By: _____

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DECLARTION UNDER 37 C.F.R. 1.132 OF STEPHEN R WEDGE

I, Stephen R. Wedge of AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK, declare that:

1. I graduated from the University of Keele, Staffordshire, UK with a Ph.D. in Cancer Pharmacology in 1991. From October 1996 until the present I have been employed by AstraZeneca UK, and currently hold the position of Senior Principal Scientist, overseeing work in the early and late stages of anticancer drug development and leading the company's global strategy in *in vivo* model development. I was a key member of the team that discovered AZD2171 (Wedge S.R. *et al.*, AZD2171: a highly potent, orally bioavailable, Vascular Endothelial Growth Factor Receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer Res.: 65 (10); 4389 – 4400, 2005) and supervised additional preclinical work on the compound following its entry into development.

2. I am familiar with the specification of published International patent application WO 2005/092385, which is a part of AstraZeneca Case 101417, and I am informed that the text of the specification of the subject US patent application 10/594,234 is the same as the text of the published International patent application. I am the inventor named on the subject application and it is my understanding that AstraZeneca AB is the assignee of record in the United States.

3. In my position as Senior Principal Scientist I am familiar with the biological assay that was carried out and reported in the subject US patent application 10/594,234, and the presentation of that data in Figures 1 and 2 of that application.

4. The following description of the assay and table of comparative biological data that was produced by that assay were obtained from the records of Case 101417, which records are maintained in the normal course of business of AstraZeneca. I hereby verify that this description of the assay is consistent with the description of the assay in the subject US patent application, and that this comparative data was used in the preparation of Figures 1 and 2 of that application. I have reviewed this biological assay and data, and further confirm that this comparative data is of statistical significance as reported on the respective Figures, and confirm the conclusion reached at the end of the following description:

Description of Biological Assay

MX-1 human breast tumour xenograft model

Tumour implantation procedures were performed on mice of at least 4 weeks of age. Human tumour xenografts were grown in female athymic (nu/nu genotype, Swiss) mice. MX-1 tumour fragments were implanted into athymic mice and allowed to grow to 0.7-1cm^3 to provide donor tumour tissue. The donor tumours were surgically excised and smaller tumour fragments (20-30 mg) were implanted subcutaneously (s.c.) in the right flanks of the experimental athymic mice. Twenty days after tumour fragment implantation, when the mean tumour volume was 0.2cm^3, randomisation was carried out (15 animals/group). Animals were treated with either docetaxel (10mg/kg, intravenously (i.v.) once weekly) or AZD2171 (1.5mg/kg or 3mg/kg, orally (p.o.) once daily) or drug vehicle (orally (p.o.) once daily) for the duration of the study. An additional group of animals (n=15) received a combination of docetaxel and AZD2171, using the same doses and schedules as used for single agent treatment. On days where animals received both AZD2171 and docetaxel the docetaxel was administered 2 hours after oral dosing with AZD2171.

Tumour volumes were assessed at least twice weekly by bilateral Vernier caliper measurement. Growth inhibition from the start of treatment was assessed

by comparison of the differences in tumour volume between control and treated groups. The effects of combination treatment were assessed by comparing tumour growth in the group of animals receiving docetaxel plus AZD2171 with the tumour growth in the groups where animals received single agent therapy alone.

Statistical significance was evaluated using a one-tailed two-sample t-test. To remove any size dependency before statistical evaluation (the variance in the mean tumour volume data increases proportionally with volume and is therefore disproportionate between groups), data was log-transformed prior to statistical evaluation. The data for combination studies wherein AZD2171 was dosed at 3 or 1.5mg/kg is shown in Figures 1 and 2. The growth inhibition of tumours was significantly greater with the combination of the two agents, AZD2171 and docetaxel, than with either agent alone.

Data Produced From The Above Assay

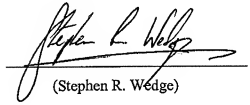
Comparative data produced from this assay is presented in the following table:

Test	Time post tumour cell injection (days)	20	22	25	28	32	35	39	41
Vehicle	Mean tumour volume (mm^3)	202.13	229.71	353.70	429.71	730.79	905.00	1174.41	1576.08
	SD	113.65	125.89	205.58	183.32	326.95	433.68	612.51	787.77
AZD2171, 3 mg/kg	Mean tumour volume (mm^3)	200.15	237.14	330.66	350.58	501.42	505.64	492.72	653.76
	SD	111.73	147.89	174.97	195.61	323.40	309.58	312.66	426.13
AZD2171, 1.5 mg/kg	Mean tumour volume (mm^3)	202.16	264.17	314.76	352.84	501.69	548.54	651.68	721.66
	SD	111.10	152.34	195.10	230.92	324.69	350.18	527.49	562.98
AZD2171, 3 mg/kg + Docetaxel, 10 mg/kg	Mean tumour volume (mm^3)	202.61	269.20	236.74	131.19	88.55	83.31	52.05	48.80
	SD	113.44	154.22	138.29	91.29	90.68	111.06	74.26	74.68
AZD2171, 1.5 mg/kg + Docetaxel, 10 mg/kg	Mean tumour volume (mm^3)	206.34	265.58	214.85	142.35	117.94	118.28	73.32	79.49
	SD	124.45	178.27	111.35	75.80	79.60	110.47	77.95	88.83
Docetaxel, 10 mg/kg	Mean tumour volume (mm^3)	206.52	264.74	250.16	197.25	163.21	195.00	142.27	200.90
	SD	124.62	130.46	158.15	144.93	100.75	159.90	131.20	183.87

5. The data presented in the above table was used in the preparation of Figures 1 and 2 in the subject application. The data from the comparative test using 3mg/kg AZD2171 and 10mg/kg docetaxel is plotted in Figure 1, and the data from the comparative test using 1.5mg/kg

AZD2171 and 10mg/kg docetaxel is plotted in Figure 2. The data, and Figures 1 and 2, show that the growth inhibition of tumours in both comparative tests was significantly greater with the combination of AZD2171 and docetaxel than with either AZD2171 or docetaxel used alone. The result is of significance, since AZD2171 inhibits VEGF receptor signaling and has been shown to reduce tumour vascular density and perfusion in preclinical tumour models. This property of AZD2171 may have been anticipated to reduce the delivery of docetaxel to the tumour cells and thereby potentially diminish its antitumour activity. However, an enhanced anti-tumour activity was observed when AZD2171 was administered chronically in combination with 3 cycles of docetaxel therapy.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punished by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature: 

(Stephen R. Wedge)

Date: 11th FEBRUARY 2009